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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,215	10/06/2000	Yasir Skeiky	14058-008010US	2519

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,215	SKEIKY ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,11,13-16,27-29 and 31* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☒ Claim(s) *11* is/are ~~allowed~~. free of cited art

6)☒ Claim(s) *1-6,10,13-16,27-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

The response filed March 26, 2003 (Paper No. 15) cancels claims 7-9, 12, 17-26 and 30, amends claims 1, 10-11, 13 and 27. The following Office action is applicable to pending claims 1-6, 10-11, 13-16, 27-29 and 31.

The grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Drawings

Drawing (Figures 1-9) filed 4 March 2003 have been approved by US PTO drafting.

IDS

Please note that Applicants' submission of IDS filed 19 August 2002 (Paper No. 13) is incomplete since it contains no legible copies of each foreign patent, which caused it to be listed on IDS. References An through AR have been lined through. Reference Am has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New grounds of rejection.

The claims 1-2, 3, 5, 10, 13-16, 27-29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Skeiky Y. et al. (US Pat. No. 6544522).

Skeiky et al. teach a recombinant polynucleotide (SEQ ID NO:1) encoding a fusion protein comprising two antigens, *i.e.*, Ra12 (antigen 1) polynucleotide and the heterologous sequence that structurally differs from the Ra12 sequence, *i.e.*, Ra35, (antigen 2), wherein the R12 polynucleotide (nucleotides 53-458) encodes Ra12 polypeptide and located 5' to the Ra35 polypeptide sequence, as applied to claims 1-2 of the instant application. Note that Skeiky's polynucleotide (SEQ ID NO:1) includes an additional heterologous sequence (nucleotides 1-62). Since the claim 1 of the instant application recites open-ended language, *i.e.*, "the recombinant nucleic acid molecule comprising ...", the Skeiky et al. teaching meets the limitation of claim 13 and anticipates the current invention set forth in claim 1.

Skeiky et al. teach that the coding sequences of each antigen in the fusion protein are joined at their amino- or carboxy-terminus via a peptide bond in any order; alternatively, the antigens are connected by a flexible linker peptide sequence (see column 5, lines 51-57), as applied to claim 3 of the current application.

Skeiky et al. teach an affinity tag, i.e., $(His)_6$-tag, that is linked to the fusion polypeptide, as applied to claim 5 of the instant application.

Skeiky et al. teach the recombinant polynucleotide comprising a Ra12 polynucleotide sequences (nucleotides 63-152) encoding a peptide sequence (amino acid residues 8-37), which reads on nucleotide sequence SEQ ID NO:17 of the instant application, as applied to claim 10 of the current application.

Skeiky et al. teach the recombinant polynucleotide comprising a Ra12 polynucleotide sequences (nucleotides 63-458) encoding a peptide sequence (amino acid residues 8-139), which

reads on peptide sequence of SEQ ID NO:4 of the instant application (see also the patent column 2, line 43-45, and Figure 1A). Skeiky's polynucleotide (SEQ ID NO:1) includes an additional heterologous sequence (nucleotides 1-62). Since the claim 13 of the instant application recites open-ended language, *i.e.*, "the recombinant nucleic acid molecule comprising ...", the Skeiky et al. teaching meets the limitation of claim 13 and anticipates the current invention set forth in claim 13.

Skeiky et al. teach host-expression vector system including a promoter operably linked to the constructed recombinant polynucleotide (see column 6,lines 27-65), and a host cell, e.g., *E.coli*. (see column 6, line 30), as applied to claims 14-16 of the current application.

Also, Skeiky et al. teach a method of producing a fusion polypeptide comprising expressing in a host cell the recombinant polynucleotide (see the patent SEQ IDS NO: 1) encoding a fusion protein comprising a Ra12 polypeptide, wherein the Ra12 polypetide is encode by the nucleotide sequence from nucleotides 63 to 458 of SEQ ID NO:1, (see column 6, line 4 through column 7, line 24), as applied to claims 27. Inasmuch as Skeiky et al. also teach constructing the fusion polypeptide with the His-tag (see the statement *supra*), the Skeiky patent is applied to claim 28 of the instant application.

Further, Skeiky et al. teach a method of purification of the expressed fusion protein, e.g., expressed in *E.coli*. (see column 6, line 30, and column 7, lines 25-47), as applied to claims 29 and 31 of the current application.

Therfore, Skeiky et al. anticipate claims 1-3, 5, 10, 13-16, 27-29 and 31 of the instant application.

Claim Rejections - 35 USC §103

The claims 1-6, 10, 13-16, 27-29 and 31 are rejected under 35 U.S.C. 103 (a) as being obvious over Reed, S. G. *et al.* (WO 9709428) taken with Skeiky et al. (US Pat. No. 6544522).

Reed *et al.* teach the TbRa12 polynucleotide (see page 6, line 12) of SEQ ID NO:4 wherein the sequence of nucleotides 11-406 encodes the amino acid sequence of SEQ ID NO:66 (residues 1-132) that is identical to SEQ ID NO:4 polypeptide (residues 1-132) of the instant application. In addition, Reed et al. teach use of immunogenic polypeptide (antigen), e.g., TbRa12 encoded by DNA of SEQ ID NO:4 (see page 4, lines 20-22), to make fusion protein, e.g., fusion between the disclosed antigen polypeptide (e.g., Ra12) and a N-terminal sequence (see page 18, lines 27-30), or fusion with two or more the disclosed antigen polypeptides (see page 22,lines 15-17) in order to induce protective immunity against tuberculosis in a patient (see page 22, lines 15-17 and page 5, lines 6-8), as applied to claims 1-2, 10, 13 and 27 of the instant application.

Also, Reed et al. teach a peptide linker in the fusion polypeptide (see pages 21- 22), as applied to claim 3 of the current application.

Yet, Reed et al. do not explicitly teach a recombinant DNA molecule comprising TbRa12 polynucleotide to produce the fusion protein, e.g., fusion molecule comprising plural antigen polypeptides and production of the fusion thereof.

Skeiky et al. teach a recombinant polynucleotide (SEQ ID NO:1) encoding a fusion protein comprising two antigens, *i.e.*, Ra12 (antigen 1) polynucleotide and the heterologous sequence that structurally differs from the Ra12 sequence, *i.e.*, Ra35, (antigen 2), wherein the

R12 polynucleotide (nucleotides 53-458) encodes Ra12 polypeptide and located 5' to the Ra35 polypeptide sequence, as applied to claims 1-2 of the instant application.

Skeiky et al. teach that the coding sequences of each antigen in the fusion protein are joined at their amino- or carboxy-terminus via a peptide bond in any order; alternatively, the antigens are connected by a flexible linker peptide sequence (see column 5, lines 51-57), as applied to claims 3 and 4 of the current application.

Skeiky et al. teach an affinity tag, i.e., $(His)_6$-tag, that is linked to the fusion polypeptide, as applied to claim 5 of the instant application.

Skeiky et al. teach the recombinant polynucleotide comprising a Ra12 polynucleotide sequences (nucleotides 63-152) encoding a peptide sequence (amino acid residues 8-37), which reads on nucleotide sequence SEQ ID NO:17 of the instant application, as applied to claim 10 of the current application.

Skeiky et al. teach the recombinant polynucleotide comprising a Ra12 polynucleotide sequences (nucleotides 63-458) encoding a peptide sequence (amino acid residues 8-139), which reads on peptide sequence of SEQ ID NO:4 of the instant application (see also the patent column 2, line 43-45, and Figure 1A). Skeiky's polynucleotide (SEQ ID NO:1) includes an additional heterologous sequence (nucleotides 1-62). Since the claim 13 of the instant application recites open-ended language, *i.e.*, "the recombinant nucleic acid molecule comprising ...", the Skeiky et al. teaching meets the limitation of claim 13 and anticipates the current invention set forth in claim 13.

Skeiky et al. teach host-expression vector system including a promoter operably linked to the constructed recombinant polynucleotide (see column 6,lines 27-65), and a host cell, e.g., *E.coli.* (see column 6, line 30), as applied to claims 14-16 of the current application.

Skeiky et al. teach a method of producing a fusion polypeptide comprising expressing in a host cell the recombinant polynucleotide (see the patent SEQ IDS NO: 1) encoding a fusion protein comprising a Ra12 polypeptide, wherein the Ra12 polypetide is encode by the nucleotide sequence from nucleotides 63 to 458 of SEQ ID NO:1, (see column 6, line 4 through column 7, line 24), as applied to claims 27. Inasmuch as Skeiky et al. also teach constructing the fusion polypeptide with the His-tag (see the statement *supra*), the Skeiky patent is applied to claim 28 of the instant application.

Skeiky et al. teach a method of purification of the expressed fusion protein, e.g., expressed in *E.coli.* (see column 6, line 30, and column 7, lines 25-47), as applied to claims 29 and 31 of the current application.

Skeiky et al. teach the linker peptide joined at their amino terminus (see column 5, line 51-53) and that a cleavage site can be introduced into the fusion protein (see column 7, lines 21-24). It would be obvious to the skilled artisan to engineer a peptide linker sequence in such a way that the linker contains a proteolytic site, which is located at between the His-tag and the interest polypeptide in order to cleave off the constructed His-tag as taught by Yan et al. (see Page 272, "*cleavage and isolation of His-tagged peptide*") so that purified fusion protein would be His-tag free, and the skilled artisan would have arrived claim 4 of the current application. Please note that because claim 1 from which claim 4 depends recites that a recombinant polynucleotide encoding a fusion protein *comprises* a Ra12 sequence and *a heterologous* sequence, wherein

"comprises" is open-ended, the Skeiky et al. teaching in respect to fusion between Ra12 sequence and a heterologous His-tar sequence as stated above meets the limitation set forth in claims 1 and 4 of the instant application.

One of ordinary skill in the art would have combined the teachings of Reed et al. and Skeiky et al. because of the following reasons: (i) Reed et al. teach the open-reading frame sequence of Ra12 (an antigen polypeptide) and teach how to make the fusion protein *via* recombinant technique (see page 21, lines 8-21), (ii) Skeiky et al. teach not only that fusion product between Ra12 and the other antigen polypeptide(s) allowing production of the recombinant fusion protein that retain the immunogenicity and antigenicity of their individual components, but also teach making the fusion protein (see columns 11-12); the fusion protein functions as an immunogen to elicit subject immunity to *M. tuberculosis* (see column 2, lines 5-27, and see also the motivation stated *supra*), and teach a recombinant polynucleotide (SEQ ID NO:1) encoding a fusion protein comprising two antigens, *i.e.*, Ra12 (antigen 1) polynucleotide and the heterologous sequence that structurally differs from the Ra12 sequence, *i.e.*, Ra35, (antigen 2) [wherein the R12 polynucleotide encodes the amino acid sequence (see the patent SEQ ID NO:2 from residue 8 to residue 139) that is identical to the residues 1-132 of SEQ ID NO:4 of the current application (see also the patent column 2, line 43-45, and Figure 1A)]; and (iii) also Skeiky et al. teach the motivation of producing the fusion protein comprising Ra12, *i.e.*, the fusion product consisting of two antigen polypeptides is used in a vaccine formulation with an adjuvant to afford long-term protection in animals against development of tuberculosis (see column 2, lines 15-27).

When combined, given the above motivation, one of ordinary skill in the art would have successfully arrived the current invention, *i.e.*, producing a recombinant polynucleotide that

encodes a fusion polypeptide comprising a Ra12 amino acid sequence consisting of SEQ ID NO:4 of the current application and heterologous sequence(s), e.g., the other antigen polypetide to *M. tuberculosis* or/and the His-tag sequence, expressing the fusion construct in a host-expression vector system as taught by Skeiky et al. (see the foregoing statement), and purifying the expression product, *i.e.*, the fusion polypeptide thereof. Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Conclusion

Claims 1-6, 10, 13-16, 27-29 and 31 are not allowed, and claim 11 is free from prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

April 14, 2003

Christopher S. F. Low

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